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MEDITERRANEAN FEVER, AND SOME
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THE RELATIONSHIP OF KALA-AZAR WITH MEDITERRANEAN FEVER, AND SOME DE- TAILS OF THE HÆMATOLOGY OF THE LATTER.

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We are indebted to the Director-General Medical Department, Admiralty, for his courtesy in forwarding this important paper.

In the JOURNAL OF TROPICAL MEDICINE of January 1st, 1903, Dr. C. A. Bentley has communicated a very powerful paper on the subject of kala-azar as seen by him in Assam.

After very exhaustively analysing the epidemiological, clinical, and microscopical features of the disease, with the serum reactions obtained in a small number of cases, he comes to the conclusion that "whatever else it may be, kala-azar is essentially Malta (Mediterranean) Fever"; he also states that no detailed study appears to have been made of the hæmatology of Malta fever, beyond that Bruce gives the average number of red cells present at 3,500,000, this important subject having been neglected by most investigators.

It is, therefore, partly for the purpose of filling in this gap that I have thought it useful to bring forward a number of observations bearing on this point, made during the last three years while in charge of wards in this Hospital to a great extent given up to the treatment of cases of Mediterranean fever, so prevalent in the Navy.

Though fully appreciating the weight of the facts and arguments brought forward by Dr. Bentley, yet there appear to me to be some fallacies in the deductions. It

is true that the similarity of the course, the undulant and prolonged intermittent type of the fever, the rheumatic pains, and the sweats, bear a close resemblance to the undulant fever of Hughes, yet all these might be due to some other bacterial infection, giving rise to a chronic intoxication other than that produced by the *Micrococcus Melitensis*. That the specific cause is closely allied is highly probable, but there seem to be differences so marked, that it is difficult to think, as Dr. Bentley evidently does, that it is only an alteration of the effects brought about by the same organism, whose toxicity and infectivity have so altered as to produce such a wide-spreading fatal disease as kala-azar, and makes one wish for further confirmation of the serum reaction test, applied to a large series of cases, before definitely accepting the theory that the causative organism is the *Micrococcus Melitensis* of Bruce. We know, of course, that various races placed under changed local and climatic conditions react very differently to any particular organism; markedly for instance "Plague," at one place, so rapidly spreading and fatal, at another being more easily controlled and having a low mortality. We should therefore be prepared for considerable alterations in the results of an infection of the *Micrococcus Melitensis*, if introduced into a poorly fed, susceptible community of natives living in a hot climate.

The chief points of difference appear to be:—

(1) The greater degree of infectivity and more rapid diffusion.

(2) The high mortality.

(3) The more constant hypertrophy of the liver and spleen.

(4) The greater degree of emaciation and pigmentation produced.

(5) The absence of those neuralgias and peripheral neuritic symptoms, so important in Mediterranean fever.

The points of similarity are, the long course of irregular fever, the sweats, the rheumatic pains, the secondary anæmia, with epistaxis, &c., and the positive reaction of the serum in eight cases.

(1) With regard to the infectivity of Mediterranean fever, it is fairly well accepted that the disease can be found under a great variety of conditions, that it is not limited to the villages along the coast of the Mediterranean, where stagnation of sewage in more or less closed harbours is apt to occur, but is also prevalent in the villages situated in the more agricultural districts. That it is contracted without the patient having been in any known infected dwelling is evident by the number of men in the Navy who go down with the disease who have not landed for long periods before the onset; yet, on the other hand, one hears of ships, and even cabins in ships, which hold extremely bad reputations; that patients collected together in wards do not communicate the disease to the healthy, though cases may occur in the building, if in the endemic area (Malta Hospital), the disease being "endemic and sporadic."

In kala-azar, the disease is much more epidemic in character, marching from place to place as an immunity is established, but destroying large numbers as it goes, and being also markedly communicable from person to person.

(2) *The high mortality.*—There is no record of anything

like the mortality of kala-azar in the districts in which Mediterranean fever is endemic. Dr. Bentley thinks that "interference with livelihood," is a possible explanation, but this does not, it seems to me, apply to children, who suffer so severely.

(3) *The hypertrophy of liver and spleen.*—Here we have one of the most important differences; the big belly and large organs are not found in the usual run of Europeans suffering from Mediterranean fever, and in the prolonged cachexia induced by the fever it is quite rare to be able to feel the spleen; even when percussed out during the febrile periods it is found to be only slightly enlarged, there being then a general congested condition of the organs.

The enlargement of the liver, too, is never of any great degree, either during the febrile attacks or afterwards.

(4) *Emaciation and pigmentation.*—In Mediterranean fever there is, during the protracted fever which may last, and often does, for four months without any marked intermission, as one would expect, a progressive loss of flesh and a general shrinkage of the tissues but in those long cases, where the intermittent mild form of fever with a temperature of 99° to 100° in the evening runs on to years, the patient never being quite well, the emaciation is not a very marked feature.

(5) *Neuroses.*—In almost all prolonged cases of Mediterranean fever the neuralgic pains are perhaps the most marked symptoms, singling out certain nerves and remaining with great persistency; in fact it is owing to the crippling effect of these attacks of neuritis that the greater number of invalids from the Service are due, the toxin apparently selecting these tissues in preference to any others, and owing to the pain so produced there follows loss of sleep, loss of appetite, and a general despondency which protracts recovery so much.

(6) *Anæmia.*—With regard to the secondary anæmia found in Mediterranean fever, the importance cannot be too much borne in mind, for if the profound blood changes are once induced, it means that the patient will be more or less of a chronic invalid for years.

Generally speaking the changes are:—

During the actual febrile attacks a great reduction in the number of the red cells, which may fall to 2,800,000 per cmm., a loss of hæmoglobin of the individual cells, and alteration in size and shape, with a slight diminution of the white cells. During the following mild febrile cachexia there is a rise in the number of the red cells to nearly normal, but they are still very, very thin and deformed, microcytes being abundant, a reduced quantity of hæmoglobin is present, and generally numerous blood plates; nucleated reds I have never seen. The white cells also rise in total numbers, but it is seen that the relative number of the active phagocytic polymorphonuclear leucocytes is reduced, with an increase of the large mononuclear lymphocytes. There is no eosinophilia.

Further investigation proved that (1) not only are the active phagocytic cells much reduced in number, but that their phagocytic power also is diminished; (2) the useful products of these cells in the blood serum is deficient, and that the bactericidal properties of the blood are reduced, accounting for the frequency of

relapses and liability of reinfection if returning to an endemic neighbourhood. *Vide British Medical Journal*, September 20th, 1902.

A SERIES OF BLOOD COUNTS IN MEDITERRANEAN FEVER CASES MADE BY THOMA ZEISS METHOD, AND TAKEN ABOUT EVERY FORTNIGHT.

CASE.		RED.	WHITE.	
1	Acute with repeated relapses	3,800,000 2,800,000 3,200,000 4,700,000	6,600 per cmm.	
			Colour index 60 per cent.	
2	Chronic case; mild relapses	4,800,000 4,800,000 4,340,000		
3	Acute case; repeated relapses, epistaxis, and otorrhœa	2,800,000 3,000,000 4,400,000 5,120,000	2,140 1,600	
			Colour index 55 per cent.	
4	Chronic case ..	4,320,000 4,240,000	3,600 2,160	
5	Chronic case 18 months; acute relapse	3,280,000 3,500,000	4,960 4,800	
			Colour index 70 per cent.	
6	Acute case; repeated relapses	2,720,000 3,200,000 4,640,000 4,320,000	2,400 5,700 5,600	
			Local abscess, Nephritis. Colour index 60 per cent.	
7	Chronic case ..	6,000,000 5,200,000 5,200,000	5,360	
			Colour index 65 per cent.	
8	Chronic cachexia 14 months	5,200,000	6,400	
9	Chronic cachexia 12 months	4,800,000	7,000	
10	Chronic cachexia 6 months	5,200,000	4,300	

TABLE GIVING THE RELATIVE COUNTS OF THE WHITE CELLS IN MEDITERRANEAN FEVER.

Case	Neutrophils	Lymphocytes	Eosinophiles	Per cent. of Neutrophils	Remarks
1. Acute ..	100	98	2	50	Poikilocytes and blood plates abundant.
	100	150	3	46	
	100	124	2	45	
	100	111	3	48	
2. Chronic ..	100	45	—	69	Red cells fairly normal, few platelets.
	100	64	5	62	
	100	101	7	51	
3. Cachexia ..	100	40	3	72	No marked anæmia.
4. Acute ..	100	63	1	62	Marked anæmia and change in size and shape of red cells.
	100	75	—	58	
	100	92	1	53	
	100	83	2	55	
	100	83	1	55	
5. Chronic ..	100	149	1	42	Great hydræmia.
6. Acute ..	100	87	3	52	Great anæmia.
	50	52	1	49	
7. Convalescent	100	68	4	76	No anæmia.
8. Chronic ..	100	143	8	43	Great anæmia.
9. Chronic ..	100	108	2	48	Great anæmia.
	100	92	—	53	
	50	69	4	44	
10. Chronic; 2 years' duration	100	50	2	67	Red cells very irregular and pale plates abundant; great anæmia.
	100	74	5	58	
	60	72	1	48	
	100	75	6	57	
	100	62	1	63	
	100	65	4	61	
	100	96	4	52	

TABLE GIVING THE RELATIVE COUNTS OF THE WHITE CELLS IN MEDITERRANEAN FEVER—continued.

Case	Neutrophils	Lymphocytes	Eosinophiles	Per cent. of Neutrophils	Remarks
11. Acute ..	100	130	2	44	Profound blood changes
	100	165	3	39	
12. Acute ..	100	125	1	45	Plates abundant, cells very pale.
	100	108	—	49	
	100	159	—	39	
	100	162	1	39	
13. Cachexia ..	100	52	3	66	Little anæmia.
	100	34	1	75	
	100	37	4	74	
14. Chronic ..	100	120	—	46	
15. Acute ..	100	103	1	50	Cells pale, plates abundant.
	100	89	4	53	
16. Chronic ..	100	72	1	59	
17. Acute ..	100	94	—	53	Cells pale, irregular in shape.
	100	114	1	47	
	100	127	—	49	
	100	96	6	51	
18. Acute relapse	90	109	—	46	Great anæmia.
	100	166	1	38	
	100	205	1	34	
	100	180	1	36	
	100	179	1	37	
19. Chronic ..	100	103	4	49	Great anæmia.
	100	79	1	57	
	100	98	2	50	
	100	61	2	62	
20. Acute ..	100	136	—	43	
Chronic ..	100	86	—	60	Marked anæmia.
	100	72	3	59	
21. Chronic ..	100	85	3	55	
22. Mild ..	100	52	2	66	No anæmia.
23. Chronic ..	100	112	—	48	Marked anæmia.
24. Chronic ..	100	105	7	49	Marked anæmia.
	100	149	—	41	
25. Chronic ..	100	148	—	41	R. C. very pale.
26. Chronic ..	100	76	6	57	
27. Chronic ..	100	84	2	55	

The average per centage of polymorphonuclear leucocytes in twenty counts of malaria with crescents present in the blood was 55 per cent.

In cachexia following malarial fever, where no parasites could be detected, it was about 58 in twenty counts. The average in six cases of tuberculosis of lung was 39 per cent.

The average of three normal bloods examined was 73 per cent.

The characters of the blood with regard to its cellular constituents are more or less common to most secondary anæmias, being found in phthisis and malarial cachexias, and are not, I think, of much value in connecting the disease of kala-azar with Mediterranean fever.

In conclusion, it appears that the case of the identity of the two diseases is "not proven," and until further corroborative evidence from serum reactions with the *Micrococcus Melitensis* is forthcoming, it would be well to still retain in our nomenclature the former as an independent disease.

WE congratulate Sir William Hooper, K.C.S.I., President of the Medical Board at the India Office, upon the well-deserved honour recently bestowed upon him.

